REMARKS

Claims 4, 6, 8, 9, and 11 remain in the application. Claims 8, 9, and 11 are currently withdrawn. Favorable reconsideration is respectfully requested.

Rejection of Claims 4 and 6 Under 35 USC §112, Second Paragraph:

This rejection is believed to have been overcome by appropriate amendment to the claims, made in accordance with the Examiner's recommendation. The errant word "and" between the chemical structures in Claims 4 and 6 has been deleted.

Withdrawal of the rejection is respectfully requested.

Rejections Under §101 and §112, First Paragraph (Enablement):

Regarding the rejections under §101 (utility) and §112, first paragraph (enablement), Applicants respectfully traverse the continuance of this rejection.

Directly addressing the Examiner's comments with respect to the Schmitt et al. paper, Applicants submitted U.S. Patent No. 6,958,384 for the Office's consideration solely as objective evidence to rebut the Office's position. The '384 Patent was submitted to show that patent applications **contemporaneous** to the present application, and articulating **the same utility** as the present application, pass muster under both §101 and §112, first paragraph (enablement).

With regard to the Schmitt et al. paper itself, Applicants' point is three-fold:

(1) The Schmitt et al. paper **is not** contemporaneous with the filing date of the present application.

(2) Schmitt et al. did **no** testing of the compounds described therein.

(3) Schmitt et al. *hypothesized* a general utility for the compounds described therein, but Schmitt's compounds are **not** the same as the claimed compounds.

The overarching point is that the Office is citing a non-contemporaneous paper, that describes non-analogous compounds, and wherein none of the compounds were tested for any utility, to support the proposition that the entirely different set of compounds recited in the present application similarly lacks utility. Applicants respectfully submit that this use of the Schmitt et al. paper is improper.

Applicants also respectfully note that the Office states, on the record, that "a single patent does not establish that the instantly asserted utility was 'well established' such that 'a person of ordinary skill in the art would immediately appreciate why the invention was useful...' . " See the sentence spanning pages 3 and 4 of the Office Action. Yet the Office itself is relying upon a single, extremely short, non-contemporaneous paper to discredit the well established utility articulated in the application as filed.

Also, Applicants note they are not relying solely upon U.S. Patent 6,958,384 to establish utility. Applicants would like to revisit Dr. Gellman's Rule 132 Declaration, filed previously. In discounting the probative value of Dr. Gellman's Declaration, the Office stated (at page 3 of the Final Office Action dated February 1, 2007):

> However, nowhere in the instant specification can the examiner find any reference to blocking Bcl-x_L/BH3 domain interactions. If such a reference were present, with adequate guidance on performing such an experiment - in the instant specification, the compound would likely have utility, as blocking Bcl-x_L/BH3 domain interactions has a specific, substantial, and credible utility.

Applicants note that the Bcl-x_L/BH3 domain model was chosen by Dr. Gellman because the system **is well characterized and well known** to those skilled in the art. See paragraph 10 of Dr. Gellman's Rule 132 Declaration. Here, Dr. Gellman declares, in relevant part:

> Traditional "small molecule" approaches, very successful for enzyme inhibition, have been less productive for generating protein-protein interaction antogonists [citation omitted], although some recent achievements are impressive [citation omitted]. I and others have used unnatural oligomers with discrete folding propensities ("foldamers") to provide a rational basis (*i.e.* a non-random basis) to make molecules that block protein-protein interactions [citation omitted]. In the examples that follow, my co-workers and I explored this specific utility in the context of Bcl-x_L/BH3 domain interactions, a system that is attractive because there is a considerable amount of structural information on the system. Petros et al. (2004) *Biochem. Biophys. Acta* 1644:83-94.

A copy of the abstract of the Petros et al. paper is enclosed for the Examiner's review. The Petros et al. abstract indicates that (as of 2004), structural studies had been performed on six Bcl-2 family members, including both anti-apoptotic members and pro-apoptotic members. As noted by Petros et al., all of the members show a remarkably similar fold despite an overall divergence in amino acid

sequence and function (anti-apoptotic vs. pro-apoptotic). The abstract goes on to describe a host of structural characteristics then already known for this family of proteins.

The point here is that the Office has indicated that this utility (blocking of Bcl-x_L/BH3 domain interactions) is "likely" sufficient for purposes of §112, first paragraph, enablement. As evidenced by the Petros et al. paper (which is a review article) this utility was clearly well known and well established in the art. As noted earlier, an application as filed does **not** have to contain any statement of utility if the claimed invention has a well-established, specific, substantial, and credible utility. Applicants submitted Dr. Gellman's Declaration earlier to provide objective evidence on this point; to show the existence of a well-established utility. *See* MPEP §2107.01(II). U.S. Patent 6,958,384 (and the earlier-submitted Seebach et al. paper) was cited solely to bolster the point. Applicants therefore respectfully submit that the application as filed articulates a well-established, specific, substantial, and credible utility for the claimed invention.

The Kim et al. paper, while contemporaneous to the present application, uses different compounds from those claimed for a different utility. The utility Kim et al. were trying to establish was to create a ligand for specific for profilin. This utility is different than what would be the analogous utility in the present application, namely, to disrupt the interaction of profilin with its α-polypeptide binding partner.

Applicants therefore request that the rejections under §101 (utility) and §112, first paragraph (enablement) be withdrawn.

Rejection of Claims 4 and 6 Under §112, First Paragraph (Written Description):

Applicants respectfully traverse this rejection.

The compounds have been illustrated by way of both complete structures and partial structures (*i.e.*, Markush groups). The specification as filed contains an extensive description of how to make the compounds, extending from page 22 to page 116 of the application as filed. Actual working examples of how to make and use the compounds are described in the Examples section, which starts at page 55 and extends to the end of the specification (page 116).

The compounds are all of the same structural genus: non-natural polypeptides containing specifically recited, cyclically-constrained beta-amino acids. All of the recited monomers are linked together in the same exact fashion - via amide bonds. The amino group of one monomer reacts with the carboxyl group of another to yield a polypeptidic bond. These bonds are extremely well understood. Both solution phase peptide synthesis and solid phase peptide synthesis are described in the application as filed. See page 55 *et seq.* of the application as filed.

Alpha-amino acids are well known, and thus there is no requirement that they be described in any detail in the application as filed. The beta- and gamma-amino acid residues that are encompassed by the claims are specifically set forth in the claims and described in great length in the application as filed.

The Office is rejecting the claims under the written description requirement, in part, for failing to provide what it considers to be a sufficient number of representative examples. On that basis alone, Applicants respectfully submit that the rejection is improper.

As a threshold consideration, there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. See MPEP §2163 and *In re Wertheim*, 191 USPQ 90 at page 97 (CCPA 1976): "We are of the opinion that the PTO has the initial burden of presenting evidence or reasons why **persons skilled in the art would not recognize** in the disclosure a description of the invention defined by the claims." (Emphasis added.) Note that the written description analysis is based upon what a person skilled in the art would recognize. On this basis, Applicants note that the claims recite a series of structurally related compounds comprised of explicitly recited monomers, all of which can be linked together using the same chemistry. The chemistry required to make the monomers is described in 50+ pages of working examples, and both solid phase and solution phase peptide synthesis (which is used to link the monomers) is both described in the specification and exceedingly well known to those skilled in the art.

Applicants further traverse this rejection because both the case law and MPEP §2163 indicate that the written description requirement for a claimed genus may be satisfied by describing:

(a) "A representative number" of species by actual reduction to practice. On this point, see compounds 16-19 at page 95, compounds 21, 22, 24, and 25 at page 96, compound 27 at page 97, compounds 28-30 at page 98, compound 33 at page 99, compounds 34-36 at page 100, compounds 38 and 39 at page 101, compounds 40 and 41 at page 102, compound 42 at page 103, and compounds 43-46 at page 104. These are all compounds that were reduced to practice, not merely prophetic examples. See page 111 *et seq.* for the NMR spectra for these compounds.

(b) By disclosing "relevant, identifying characteristics," such as by describing structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics. On this point, Applicants again refer to the truly extensive description of the chemistry required to fabricate the monomers, and the fact that the monomers are all amino acids. They are linked together using the same well-known linking chemistry used for alpha amino acids. This chemistry is described in great detail in the passage starting at page 109 of the application as filed.

In short, all that is required to satisfy the written description requirement of §112 is to show, essentially by any descriptive or illustrative means, that the Applicant was in possession of the claimed genus. See MPEP §2163(3)(a) and *The Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398, at page 1406 (the *Eli Lilly* case).

Applicants respectfully submit that the Office's selective quotation from the *Eli Lilly* case at page 9 of the Office Action distorts the holding of the *Eli Lilly* court. The quote cited by the Office from the Lilly case is directed to "genetic material." The full passage quoted by the Office only in part begins with the prepositional phrase "In claims to genetic **material**...." The present claims, however, are not drawn to "genetic material." Applicants are not claiming a gene, or a cDNA, or a protein, or any other type of genetic material. The present claims are drawn to synthetic polypeptides fabricated entirely by synthetic means.. And all of the steps need to make the claimed compounds, as well as the materials that are to be used in those steps, are clearly described within the specification by way of example, by way of structure, and by way of general protocols that can be used to make all of the compounds encompassed by the claims.

The *Eli Lilly* quotation is inapposite in the present situation because in the *Eli Lilly* case the plaintiffs never described any aspect of the claimed human cDNA beyond the amino acid sequence it was to encode. Briefly, the claims at issue in the *Eli Lilly* case were drawn to a **human** cDNA. But the only cDNA sequence contained in the disputed specification in *Eli Lillly* was that of a **rat** cDNA analogous to the claimed **human** cDNA. In short, the Applicants in *Eli Lilly* described a rat cDNA and tried to claim an analogous human cDNA. But their specification did not describe any characteristic of the human cDNA (beyond the protein it was supposed to encode). Having failed entirely to describe any structural characteristic of the claimed **human** cDNA itself (*e.g.*, structure, formula, or physical properties, as noted in *Fiers v. Sugano/Revel* [more of which below]), the Court in *Eli Lilly* held that plaintiffs did not adequately describe a cell transformed to contain a **human** cDNA.

Unlike the *Eli Lilly* case (where the Applicants described a rat cDNA and tried to claim a human cDNA), in the present situation, the Applicants are claiming a genus of compounds that are described in great and specific detail in the application as filed, including a host of working example where the compounds were both made and characterized by NMR. The specification describes the compounds that are claimed, which was not the situation in the *Eli Lilly* case. Armed with the knowledge conveyed by the present application, the person of ordinary skill in the art would certainly comprehend that other suitable monomers beyond those specifically exemplified by way of working examples can be made using the protocols presented in the specification.

The Office's citation to *Fiers v. Sugano*, 25 USPQ2d 1601, at the bottom of page 9 of the Office Action, is also inapposite. The quote from *Fiers* provided by the Office is contained in **dictum** and **was not** the holding of the court. Contrary to Judge Lourie's quoted dictum from *Fiers*, it has **never** been the law that an Applicant must know the structure of a compound (DNA, protein, or otherwise) in order to satisfy the requirements of §112, first paragraph (written description). The controlling law in this instance is provided by *In re Fisher*, 166 USPQ 18 (CCPA 1970). In *Fisher*, the question was whether the claims of a CIP application (drawn to a protein) were entitled to the filing date of the parent application. In *Fisher*, it was undisputed that the amino acid sequence of the protein

claimed in the CIP **was not** disclosed in the parent application, and further that *Fisher* **did not** know the amino acid sequence at the time the parent application was filed (166 USPQ at 21). The only disclosure in the parent application was a process for extracting the protein from the pituitary glands of certain animals. However, an article which appeared *after* the filing of the CIP application confirmed that the claimed sequence was, in fact, the sequence of protein described in the parent application. The CCPA **held** that the claimed structure was inherent in the description contained in the parent application, and therefore the parent application described the protein to the level required by §112, first paragraph.

The situation in the present application, of course, is not so extreme. The specification contains an extensive description of how to make the compounds encompassed by the claims. Applicants therefore submit that the rejection of the claims under §112, first paragraph (written description) is untenable. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In light of the above amendment and remarks, Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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1: Biochim Biophys Acta. 2004 Mar 1;1644(2-3):83-94.

Structural biology of the Bcl-2 family of proteins.

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The proteins of the Bcl-2 family are important regulators of programmed cell death. Structural studies of Bcl-2 family members have provided many important insights into their molecular mechanism of action and how members of this family interact with one another. To date, structural studies have been performed on six Bcl-2 family members encompassing both anti- (Bcl-x(L), Bcl-2, KSHV-Bcl-2, Bcl-w) and pro-apoptotic (Bax, Bid) members. They all show a remarkably similar fold despite an overall divergence in amino acid sequence and function (pro-apoptotic versus anti-apoptotic). The three-dimensional structures of Bcl-2 family members consist of two central, predominantly hydrophobic alpha-helices surrounded by six or seven amphipathic alpha-helices of varying lengths. A long, unstructured loop is present between the first two alpha-helices. The structures of the Bcl-2 proteins show a striking similarity to the overall fold of the pore-forming domains of bacterial toxins. This finding led to experiments which demonstrated that Bcl-x(L), Bcl-2, and Bax all form pores in artificial membranes. A prominent hydrophobic groove is present on the surface of the anti-apoptotic proteins. This groove is the binding site for peptides that mimic the BH3 region of various pro-apoptotic proteins such as Bak and Bad. Structures of Bcl-x(L) in complex with these BH3 peptides showed that they bind as an amphipathic alpha-helix and make extensive hydrophobic contacts with the protein. These data have not only helped to elucidate the interactions important for hetero-dimerization of Bcl-2 family members but have also been used to guide the discovery of small molecules that block Bcl-x(L) and Bcl-2 function. In the recently determined structure of the anti-apoptotic Bcl-w protein, the protein was also found to have a hydrophobic groove on its surface capable of binding BH3-containing proteins and peptides. However, in the native protein an additional carboxy-terminal alpha-helix interacts with the hydrophobic groove. This is reminiscent of how the carboxy-terminal alpha-helix of the pro-apoptotic protein Bax binds into its hydrophobic groove. This interaction may play a regulatory role and for Bax may explain why it is found predominately in the cytoplasm prior to activation. The hydrophobic groove of the pro-apoptotic protein, Bid protein, is neither as long nor as deep as that found in Bcl-x(L), Bcl-2, or Bax. In addition, Bid contains an extra alpha-helix, which is located between alpha1 and alpha2 with respect to Bcl-x(L), Bcl-2, and Bax. Although there are still many unanswered questions regarding the exact mechanism by which the Bcl-2 family of proteins modulates apoptosis, structural studies of these proteins have deepened our understanding of apoptosis on the molecular level.

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